

7. The polypeptide [growth factor] of claim 6, comprising SEQ ID NO:23, SEQ ID NO:24 or SEQ ID NO:25.

8. The polypeptide [growth factor] of claim 6, consisting of SEQ ID NO:26, SEQ ID NO:27 or SEQ ID NO:28.

9. A composition comprising the polypeptide [growth factor] of claim 1 in a pharmaceutically acceptable preparation.

Remarks

A petition to the Commissioner to review the restriction requirement relating to the election of a single specific persephin sequence has been submitted concurrent with this response. The arguments and amendments herein made are therefore based upon the consideration that the restriction is improper and that the persephin sequences are mere species of a genus.

The corrected drawings herewith submitted do not contain new matter and are meant to comply with 37 C.F.R. Sections 1.84 and 1.1.153.

Rejections under 35 USC Section 112, first paragraph.

Claims 1-3 and 9 are rejected as lacking sufficient guidance, explanation, or written description concerning the structure of the polypeptide. Claims 2 and 3 have been cancelled, rendering the rejection of those claims moot. Claim 1 has been amended to contain the elements of claims 2-4 (claim 4 does not stand rejected under 35 USC Section 112, first paragraph), which provide detailed description of the structure of the substituted persephin, which is clearly described and enabled. Applicants believe that claim 1 and claim 9 meet the statutory requirements for patentability and request that the rejection be withdrawn.

Claims 6-8 are rejected as containing subject matter that is not enabled, particularly the polypeptide based upon the substituted human persephin of SEQ ID NO:1. All of the claimed embodiments of the polypeptide of the instant invention are fully described on the basis of their chemical structures (as SEQ ID NOS), leaving no confusion as to the subject matter of the invention or the metes and bounds of the invention. Furthermore, the specification describes in Example 1 how to make and use representative species of the claimed polypeptide. Given the high level of skill in the art, particularly the

routine nature of recombinant DNA technology and protein expression, the written description of the sequences of the claimed embodiments, and the generic method described in Example 1 of the instant specification, the method of making each and every embodiment of the claimed polypeptide is obvious.

A major component of the Examiner's enablement rejection regarding the substituted human persephin is whether the substituted human persephin operates as a growth factor. Given (1) that working examples of substituted persephins are provided in the specification, (2) that the human, mouse and rat persephins are greater than 84% identical and 94% similar (conserved substitutions permitted; see Exhibit B, which compares human, rat and mouse persephin cores), (3) that the ligand agonist assays were preformed on a *human* neuroblastoma cell line (NBL-S; see Example 3, page 34, second paragraph) and (4) that the art is replete with examples of growth factor ligands derived from one species having the ability to effect a response in another (recall that porcine and bovine insulin have been used for years to treat human insulin-dependent diabetes; also see Enokido et al., *Current Biology* 1998, 8:1019-1022, which describes at least in Figure 1 on page 1019 the ability of *human* persephin to activate *chicken* GFR α -4), the skilled artisan would reasonably expect that the substituted persephin of claims 6-8 are operable as a GFR α -1 agonist, thus having reasonable usefulness and thus being enabled.

Furthermore, the case law supports the premise that "structural *similarity* to a compound known to have a particular therapeutic or pharmacological utility [supports] an assertion of therapeutic utility for [another] compound" (emphasis added). MPEP2107.03 and *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980). Applicants contend that the human substituted persephins of claims 6-8 are sufficiently similar to the rat/murine chimera proteins to support the assertion of utility of the human substituted persephins as a GFR α -1 agonist. The skilled artisan would not reasonably doubt the utility of the human substituted persephin as a GFR α -1 agonist. Please also note that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development." See *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). Applicants hereby assert that, according to USPTO practice and the case law, the claims to the human substituted persephin meet the requirements of 35 USC Section 112, first paragraph.

Claims 1 and 5-9 have been amended to replace the term "growth factor" with the term "polypeptide." Support for this amendment can be found according to the instant specification at page 1, line 18, which states that growth factors are polypeptides. This amendment obviates the Examiner's rejection of claims 6-8 based upon the implication, albeit a correct implication, that human substituted persephin is a growth factor.

Rejections under 35 USC Section 112, second paragraph.

Claims 2 and 3 are rejected as being indefinite. Claims 2 and 3 have been cancelled, thereby rendering the rejection moot.

Claims 4 and 5 are rejected as being indefinite for including "non-elected" embodiments of the election. Applicants continue to assert the unity of the sequences under a single invention and have submitted a Petition to the Commissioner according to 37 C.F.R. 1.144 to review the Examiner's imposition of the restriction requirement. Applicants will defer amending claim 1 and claim 5 pending the Commissioner's decision regarding the imposition by the Examiner of the restriction requirement. The limitations of claim 4 have been incorporated in their entirety into claim 1 and claim 4 has been cancelled without disclaimer.

Rejections under 35 USC Section 102(b).

Claims 1-2 are rejected as being anticipated by Jing et al as evidenced by Worby et al. Jing et al. teaches that GDNF activates GFR α 1-RET but does not substantially activate GFR α 2-RET. Worby et al. teaches that GDNF does not bind to GFR α 3-RET. Claim 2 has been cancelled without disclaimer, thereby rendering this rejection moot. Claim 1 has been amended to contain the limitations of original claims 2-4, and is thus limited to the disclosed substituted persephins, thereby avoiding GDNF. Thus, Worby et al. and Jing et al. do not anticipate claim 1. Applicants request that the rejection of claim 1 under 35 U.S.C. Section 102(b) be withdrawn.

Claim 2 is rejected as being anticipated by Johnson et al., which discloses a chimeric protein PSP/NTN. Claim 2 has been cancelled, thereby rendering this rejection moot.

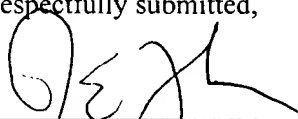
Rejections under 35 USC Section 103(a).

Claim 9 is rejected as being unpatentable over Jing et al on the basis that it would have been obvious to the skilled artisan to combine the growth factor of Jing et al. with a pharmaceutically acceptable preparation. Since claim 1 presently reads on specific substituted persephins and not on the GDNF growth factor of Jing, et al., the claimed invention is not obvious. Applicants request that the rejection of claim 9 under 35 U.S.C. Section 103(a) be withdrawn.

Conclusion

In view of the amendments made herein to the claims and the arguments put forth, Applicants believe that the claims are in a condition for allowance. Applicants respectfully request that the rejections to claim 1 and 5-9 be withdrawn and the claims allowed. If there are any other issues remaining, the Examiner is invited to call the undersigned agent.

Respectfully submitted,



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AMENDED CLAIMS

1. (Amended) A polypeptide which activates GFR α 1-RET but does not substantially activate GFR α 2-RET or GFR α 3-RET, wherein

(a) said polypeptide comprises a persephin as set forth in SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3, and further comprises substitutions in region F2a and substitutions in region F2c,

(b) the substitutions in region F2a comprise from one to eight amino acids that are either identical to region F2a of a GDNF family ligand, or contain conservative amino acid substitutions of region F2a of a GDNF family ligand,

(c) the substitutions in region F2c comprise from one to eight amino acids that are either identical to region F2c of a GDNF family ligand, or contain conservative amino acid substitutions of region F2a of a GDNF family ligand,

(d) the GDNF family ligand is a peptide selected from the list consisting of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:10.

5. (Amended) The polypeptide of claim 1, comprising SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:16.

6. (Amended) The polypeptide of claim 1, wherein the substituted persephin comprises a human persephin as set forth in SEQ ID NO:1 with substitutions for amino acid residues 63-66 selected from the group consisting of SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19, and substitutions for amino acid residues 76-82 selected from the group consisting of SEQ ID NO:20, SEQ ID NO:21, and SEQ ID NO:22.

7. The polypeptide of claim 6, comprising SEQ ID NO:23, SEQ ID NO:24 or SEQ ID NO:25.

8. The polypeptide of claim 6, consisting of SEQ ID NO:26, SEQ ID NO:27 or SEQ ID NO:28.

9. A composition comprising the polypeptide of claim 1 in a pharmaceutically acceptable preparation.